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EUROPEAN PATENT APPLICATION

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(54) **Recombinant production of novel polyketides**

(57) Novel polyketides and novel methods of efficiently producing both new and known polyketides, using recombinant technology, are disclosed. In particular, a novel host-vector system is described which is used

to produce polyketide synthases which in turn catalyze the production of a variety of polyketides.

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European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 05 00 7590

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	KHOSLA CHAITAN ET AL: "Targeted gene replacements in a Streptomyces polyketide synthase gene cluster: Role for the acyl carrier protein." MOLECULAR MICROBIOLOGY, vol. 6, no. 21, 1992, pages 3237-3249, XP000990939 ISSN: 0950-382X * abstract; figures 2,4 *	1-3,13	C12N15/52 C12N15/76 C12P19/62 C12N1/21
X	KHOSLA C ET AL: "GENETIC CONSTRUCTION AND FUNCTIONAL ANALYSIS OF HYBRID POLYKETIDE SYNTASES CONTAINING HETEROLOGOUS ACYL CARRIER PROTEINS" JOURNAL OF BACTERIOLOGY, WASHINGTON, DC, US, vol. 175, no. 8, April 1993 (1993-04), pages 2197-2204, XP002045170 ISSN: 0021-9193 * abstract; figures 1,4 *	1-3,13	
X	WO 93/13663 A (ABBOTT LAB) 22 July 1993 (1993-07-22) * claims 1-21,26 *	1-3,13	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C12P C12N
X	STROHL W R ET AL: "Expression of polyketide biosynthesis and regulatory genes in heterologous streptomycetes." JOURNAL OF INDUSTRIAL MICROBIOLOGY. APR 1991, vol. 7, no. 3, April 1991 (1991-04), pages 163-174, XP002332285 ISSN: 0169-4146 * abstract; table 1 *	1-3,13	
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The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 20 June 2005	Examiner Gurdjian, D
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure F : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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EPO FORM 1503 03.92 (P4/C03)



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 05 00 7590

DOCUMENTS CONSIDERED TO BE RELEVANT				
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)	
X	DONADIO S ET AL: "RECENT DEVELOPMENTS IN THE GENETICS OF ERYTHROMYCIN FORMATION" INDUSTRIAL MICROORGANISMS: BASIC AND APPLIED MOLECULAR GENETICS. ASM CONFERENCE ON THE GENETICS AND MOLECULAR BIOLOGY OF INDUSTRIAL MICROORGANISMS, 1992, pages 257-265, XP000607676 * abstract; figures 1,5,6 *	1-3		
D,X	BARTEL P L ET AL: "Biosynthesis of anthraquinones by interspecies cloning of actinorhodin biosynthesis genes in streptomycetes: clarification of actinorhodin gene functions." JOURNAL OF BACTERIOLOGY. SEP 1990, vol. 172, no. 9, September 1990 (1990-09), pages 4816-4826, XP002332286 ISSN: 0021-9193 * figures 1,2; tables 1,4 *	1-3		
X	STROHL WR ET AL: "SIGNIFICANCE OF ANTHRAQUINONE FORMATION RESULTING FROM THE CLONING OF ACTINORHODIN GENES IN HETEROLOGOUS STREPTOMYCETES" MOLECULAR MICROBIOLOGY, 1992, 6, 147-152, 1992, XP002332287 * abstract; figures 1-3 *	1-3,13		TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	SHERMAN DH ET AL: "FUNCTIONAL REPLACEMENT OF GENES FOR INDIVIDUAL POLYKETIDE SYNTHASE COMPONENTS IN STREPTOMYCETES-COELICOLOR A3(2) BY HETEROLOGOUS GENES FROM A DIFFERENT POLYKETIDE PATHWAY" JOURNAL OF BACTERIOLOGY, 1992, 174, 6184-6190, 1992, XP002066449 * abstract; figures 1,2; table 2 *	1-3		
-The present search report has been drawn up for all claims				
Place of search The Hague		Date of completion of the search 20 June 2005	Examiner Gurdjian, D	
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document		

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EPO FORM 1503 03/95 (P01C04)



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 05 00 7590

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	CHATER K F: "THE IMPROVING PROSPECTS FOR YIELD INCREASE BY GENETIC ENGINEERING IN ANTIBIOTIC-PRODUCING STREPTOMYCETES" BIO/TECHNOLOGY, NATURE PUBLISHING CO. NEW YORK, US, vol. 8, no. 2, 1 February 1990 (1990-02-01), pages 115-121, XP000087713 ISSN: 0733-222X * the whole document *	1-3	
D,A	HOPWOOD D A ET AL: "MOLECULAR GENETICS OF POLYKETIDES AND ITS COMPARISON TO FATTY ACID BIOSYNTHESIS" ANNUAL REVIEW OF GENETICS, ANNUAL REVIEWS INC., PALO ALTO, CA, US, vol. 24, 1990, pages 37-66, XP000929983 ISSN: 0066-4197 * the whole document *	1-4,13	
T	ZIERMANN R ET AL: "Recombinant polyketide synthesis in Streptomyces: engineering of improved host strains" BIOTECHNIQUES, EATON PUBLISHING, NATICK, US, vol. 26, no. 1, January 1999 (1999-01), pages 106-110, XP002170304 ISSN: 0736-6205 * the whole document *	1-4	
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-The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 20 June 2005	Examiner Gurdjian, D
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EPO FORM 1503 (03.82) (P04001)



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 05 00 7590

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
T	<p>TSOI C J ET AL: "COMBINATORIAL BIOSYNTHESIS OF 'UNNATURAL' NATURAL PRODUCTS: THE POLYKETIDE EXAMPLE MULTI-ENZYME SYSTEMS, SUCH AS THOSE INVOLVED IN THE BIOSYNTHESIS OF POLYKETIDES, TYPICALLY CATALYZE SEVERAL DISTINCT REACTIONS THAT ARE COMBINED IN DIFFERENT WAYS TO GENERATE DIVERSE NATURAL PRODUCTS. THE VARIABILITY" CHEMISTRY AND BIOLOGY, CURRENT BIOLOGY, LONDON, GB, vol. 2, no. 6, 1995, pages 355-362, XP000915710 ISSN: 1074-5521 * the whole document *</p> <p>-----</p>	1-4,13	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
<p>The present search report has been drawn up for all claims</p>			
Place of search		Date of completion of the search	Examiner
The Hague		20 June 2005	Gurdjian, D
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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EPO FORM 1505 01.02 (P0409)



European Patent
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Application Number

EP 05 00 7590

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1-4, 13



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LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 05 00 7590

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-4,13

host cell, deficient in a wild-type polyketide gene cluster
, with replacement polyketide gene cluster , and the
corresponding method of production of polyketides

2. claim: 5

polyketide produced by a host cell with a replacement
polyketide gene cluster

3. claims: 6-8

Recombinant vector comprising a replacement polyketide gene
cluster and an heterologous control element , and
corresponding host cell

4. claim: 9

polyketide with formula (1) , as disclosed in the
description page 31

5. claim: 10 partially

polyketide with formula 12 as disclosed page 33 of the
description

6. claims: 10,12 partially

polyketide with formula 13 as disclosed page 34 of the
description or formula (iv) as disclosed page 37 of the
description

7. claims: 10,12 partially

polyketide with formula 14,15 as disclosed page 34,35 of the
description or formula (iii) as disclosed page 37 of the
description

8. claims: 10,12 partially

polyketide with formula 16 as disclosed page 35 of the
description or formula (v) as disclosed page 38 of the
description



European Patent
Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 05 00 7590

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

9. claim: 11

polyketide compound formed by catalytic cyclization of an
enzyme-bound ketide having the formula (ii) as disclosed
page 36 of the description

20-06-2005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9313663	A	22-07-1993	NONE

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82